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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/330,903 | 06/11/99 | GONDA I | 6513/061US1 |

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| SCHNIZER,R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 8 |

**DATE MAILED:** 05/23/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

FILE COPY

| Office Action Summary | Application No. 09/330,903 | Applicant(s) Gonda et al |
|---|---|---|
| | Examiner Richard Schnizer | Group Art Unit 1632 |

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

☒ Claim(s) 1-20 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*— SEE OFFICE ACTION ON THE FOLLOWING PAGES —*

## DETAILED ACTION

An information disclosure statement was received and entered as Paper No. 6 on 2/18/00.

### *Priority*

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

In this case, claims 2, 6, and 7 of the instant application are not supported by the specification of the parent application. Specifically, the parent application, now issued as US Patent 5,906,202, makes no mention of targeting aerosols to the alveoli, or of the use of lipids or liposomes.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are indefinite because they recite a relationship between the aerodynamic diameter of aerosol particles and an airway diameter of an area of the respiratory tract, but the nature of the relationship is not disclosed. Diameters are numerical values. All numerical values are related to all other numerical values simply by their magnitudes, thus it is meaningless to require that the diameters of the particles and the airways must be related without disclosing how they must be related.

Claims 3 and 4 are indefinite because it is not clear exactly where the upper respiratory tract ends, and the central airways begin, thus one of skill in the art is not apprised of the metes and bounds of the claim.

Claims 8 and 9 are indefinite because they incorporate the extra step of heating the formulation, but do not disclose at what point in the method this step is to be executed. Specifically, is the heating performed before, or after, formation of an aerosol? Claims 8 and 9 are also indefinite because the meaning of the word "significant" is unclear in its context, and because it is not clear what characteristic of the particles is "adjusted". It is suggested that the word significant be replaced with the word "sufficient".

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5-7, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Debs (US Patent 5,756,353, effective filing date of 12/17/91).

Debs teaches methods of delivering polynucleotides preferentially to specified regions of the respiratory tract wherein liquid DNA/cationic liposome formulations are aerosolized and inhaled into the respiratory tract of a subject. See abstract; column 5, lines 51-60; column 10, lines 53-59; and column 12, lines 3-5. For delivery to the alveoli and airways, preferred particle sizes are 0.2-2.0 μm and 5-10 μm, respectively. See column 12, lines 37-61; and claims 14-16, column 16.

Thus Debs anticipates the claims.

Claims 1, 2, 6, 7, 10, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Eljamal et al (US Patent 5,994,314, effective filing date of 4/7/93).

Eljamal teaches methods of delivering polynucleotides to the lung wherein dried, powdered DNA/cationic lipid complexes are aerosolized and inhaled. The preferred aerodynamic diameter of the complexes is 1-4 μm. See abstract; column 2, lines 24-35; column 5, lines 48-57; column 6, lines 30-33; and column 7, lines 22-34. It is noted that Eljamal does not explicitly disclose targeting of the alveolar region, however this targeting is inherent in the size range of the particles (1-4 μm).

Thus Eljamal anticipates the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353, effective filing date of 12/17/91), Lloyd et al (US Patent 5,497,763, effective filing date of 5/21/93), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Debs teaches methods of delivering polynucleotides preferentially to specified regions of the respiratory tract wherein liquid DNA/cationic liposome formulations are aerosolized and inhaled into the respiratory tract of a subject. More specifically, Debs teaches that particular sites

in the lung can be targeted by varying the size of the aerosol particles, and that particle size can be controlled by selection of an appropriate nebulizer. See abstract; column 5, lines 51-60; column 10, lines 53-59; and column 12, lines 3-5. Preferred particle size for delivery to the alveoli is 0.2-2.0 μm; and for the airways or nasopharynx, preferred particle size is 5-10 μm. See column 12, lines 37-61; and claims 14-16, column 16. Debs does not teach precise ranges of 1-3, 4-6, and 7-10 μm for the alveoli, the central airways, and the upper respiratory tract, respectively.

Lloyd teaches a method for producing aerosol particles of any desired size in the range of 0.5 to 50 μm. The method involves forcing a formulation through a porous membrane, wherein the size of the aerosol particles formed is directly related to the diameter of the membrane pores. See column 24, lines 30-43.

Radhakrishnan teaches that aerosol droplets larger than 3 μm will reach the secondary bronchi, but not the alveoli. Droplets smaller than 3 μm will target the alveoli. Radhakrishnan also presents a model depicting the relationship between aerosol particle aerodynamic diameter and penetration into the respiratory tract. See Fig. 3. CH, L25-32

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the information provided in Fig. 3 of Radhakrishnan to selectively target the alveoli, central airways, or upper respiratory tract with the polynucleotide-containing aerosol particles of Debs. Although the relationship between particle diameter and lung target tissue taught by Radhakrishnan is not precisely the same as that disclosed in the instant invention, it is standard procedure, and well within the ability of one of ordinary skill, to optimize parameters such as

aerosol particle diameter in order to achieve targeting to a specific tissue. One could have relied on the teachings of Lloyd to produce particles of the appropriate size. One would have been motivated to target each of the claimed areas of the lung in order to maximize the delivery of polynucleotides to tissues *in vivo*. For example, it is well known in the art that the major obstacles to gene therapy, such as that proposed by Debs (column 1, lines 15-18), are insufficient delivery and expression of therapeutic polynucleotides. Thus one of ordinary skill in the art would seek to solve these problems by contacting as much of the respiratory tract as possible with polynucleotide-containing aerosol particles.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 8, 9, 11, 12, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lloyd et al (US Patent 5,522,385, filed 9/27/94), Eljamal et al (US Patent 5,994,314, effective filing date of 4/7/93), and Lanpher et al (US Patent 5,333,106, issued 7/26/94).

Lloyd teaches a method of delivering powdered aerosolized particles to the lung wherein particles of 0.5-12.0 μm diameter are produced by extrusion through a porous membrane with pores of 0.25-6.0 μm diameter. The aerosolized particles are heated in order to evaporate carrier and to control their size. This technique allows one to adjust particle dryness and size while accounting for environmental conditions such as relative humidity. Lloyd does not explicitly disclose targeting of the specific regions of the respiratory tract, however this targeting is inherent

in the size range of the particles produced by the method. Lloyd also does not teach delivery of polynucleotides, adjusting inspiration volume, or measuring airflow electronically.

Eljamal teaches methods of delivering polynucleotides to the lung wherein dried, powdered DNA/cationic lipid complexes are aerosolized and inhaled. The preferred aerodynamic diameter of the complexes is 1-4 μm. See abstract; column 2, lines 24-35; column 5, lines 48-57; column 6, lines 30-33; and column 7, lines 22-34.

Lanpher teaches an electronic apparatus for measuring inspiration volume and airflow, and a method for teaching patients to inspire a particular volume at a particular rate. The purpose of the apparatus and the method is to teach patients to use aerosol inhalers properly so that medication is delivered to a target site in the patient's lungs. See entire document; especially abstract; paragraph bridging columns 8 and 9; column 9, lines 33-53; and claim 1, columns 24 and 25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver polynucleotides by the method of Lloyd. One would have been motivated to do so because Lanpher teaches that polynucleotides can be delivered in an aerosol of dried powder particles, and because the method of Lloyd allows one to adjust the dryness of the particles in view of ambient conditions such as humidity.

It would have been obvious to one of ordinary skill in the art at the time of the invention to adapt the device of Lanpher in order to train patients to use the delivery method of Lloyd. One would have been motivated to do so because Lanpher teaches that many patients use inhalers

improperly, thus there is a need to effectively train them in proper technique. See paragraph bridging columns 2 and 3.

Thus the invention as a whole was *prima facie* obvious.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800

Richard Schnizer, Ph. D.